PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

United States Patent and Trademark Office
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in its capacity as elected Office

Date of mailing (day/month/year) 16 December 1998 (16.12.98)	
International application No. PCT/EP98/02999	**Applicant's or agent's file reference** P70920WO
International filing date (day/month/year) 13 May 1998 (13.05.98)	**Priority date** (day/month/year) 13 May 1997 (13.05.97)
Applicant CAWTHORNE, Michael, Anthony et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

23 November 1998 (23.11.98)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO
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1211 Geneva 20, Switzerland

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Authorized officer

Lazar Joseph Panakal

Telephone No.: (41-22) 338.83.38

CORRECTED VERSION*

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WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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A61K 38/31, 7/48

A1

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08/854,941 13 May 1997 (13.05.97) US

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(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published

With international search report.

Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: SOMATOSTATIN AND SOMATOSTATIN AGONISTS FOR DECREASING BODY WEIGHT

(57) Abstract

The present invention relates to a method of decreasing body weight in a patient. The method includes the step of administering a therapeutically effective amount of a somatostatin or a somatostatin agonist to said patient. A pharmaceutical/cosmetic composition comprises the somatostatin or somatostatin agonist. Such products are used to prepare such compositions for the reduction of body weight in a human or mammalian animal.

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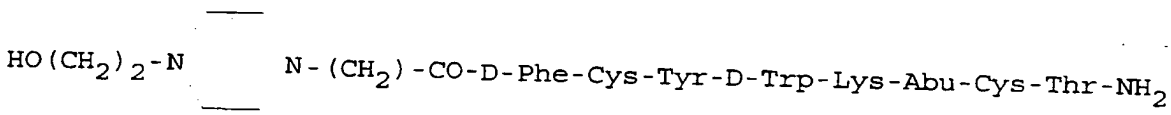

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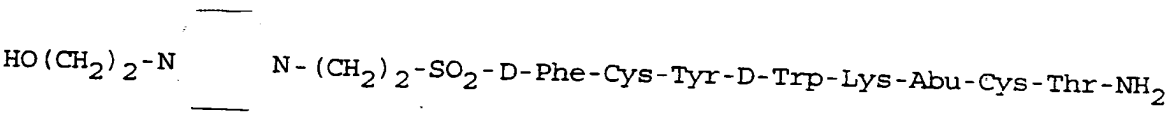

.

27. A method according to claim 1 wherein said patient is obese.

28. A method according to claim 3 wherein said patient is obese.

29. A method according to claim 4 wherein said patient is obese.

30. A method according to claim 7 wherein said patient is obese.

31. A method according to claim 8 wherein said patient is obese.

32. A method according to claim 11 wherein said patient is obese.

33. A pharmaceutical or cosmetic composition comprising a therapeutically or cosmetically effective amount of somatostatin; or a somatostatin agonist; or H-Cys-Phe-D-Trp-Lys-Thr-Phe-Cys-NH_2, wherein a disulfide bond exists between the free thiols of the two Cys residues.

34. A pharmaceutical composition as claimed in claim 33 having the features identified in any one of claims 3 to 10 and 23 to 26.

35. Use of a somatostatin, or a somatostatin agonist or H-Cys-Phe-Phe-D-Trp-Lys-Thr-Phe-Cys-NH_2, wherein a disulfide bond exists between the free thiols of the two Cys residues, in the formulation of a pharmaceutical or cosmetic composition for use in reducing excessive body weight in a human or mammalian animal.

36. Use of a somatostatin, or a somatostatin agonist according to claim 35, wherein said somatostatin or somatostatin agonist has the relevant features identified in any one of claims 3 to 10 and 23 to 26.

37. A pharmaceutical composition substantially as hereinbefore described with reference to the Examples.

09/423684

PATENT COOPERATION TREATY

REC'D 20 AUG 1999

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
P70920WO		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP98/02999	13/05/1998	13/05/1997
International Patent Classification (IPC) or national classification and IPC A61K38/31		
Applicant SOCIETE DE CONSEILS DE RECHERCHES ET ... et al		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which hav been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 2 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☒ Certain documents cited
   - VII ☒ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
23/11/1998	18.08.99
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. (+49-89) 2399-0 Tx: 523656 epmu d Fax: (+49-89) 2399-4465	Authorized officer Pilling, S Telephone No. (+49-89) 2399 8461

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP98/02999

I. Basis of the report

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

Description, pages:

1-25	as originally filed				

Claims, No.:

1-25,26 (part)	as originally filed				
26 (part),27-37	as received on	26/07/1999	with letter of	20/07/1999	

2. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-32, 35, 36
	No:	Claims	33, 34, 37
Inventive step (IS)	Yes:	Claims	7, 9,
	No:	Claims	1 to 6, 8, 10-32, 35, 36
Industrial applicability (IA)	Yes:	Claims	33-37 (for Claims 1 to 32 see paragraph 2 of SECTION V on separate sheet)
	No:	Claims	

2. Citations and explanations

see separate sheet

VI. Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

SECTION V

1. The present application relates to methods of decreasing bodyweight using somatostatin or an agonist thereof (see Claims 1 to 32), compositions comprising somatostatin or an agonist thereof (see Claims 33, 34 and 37) and the use of somatostatin or an agonist thereof in the formulation of a composition for use in reducing excessive body weight (see Claims 35 and 36).

2. Claims 1 to 32 relate at least in part to methods of treatment of the human or animal body by therapy. In this regard, for the assessment of these claims with respect to industrial applicability, no unified criteria exist in the PCT. Furthermore, patentability can be dependent on the formulation of the claims. The EPO, for example does not recognize as industrially applicable, the subject matter of claims directed to a method of treatment of the human or animal body or to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment. Therefore, no statement as to the industrial applicability of Claims 1 to 32 is made herein.

3. The documents cited in the International Search Report (ISR) are consecutively numbered D1 to D6 in the order of their listing. If not indicated otherwise, reference is made to the passages cited in said ISR.

4. The following document is additionally cited herein;

   D7: H-J S Huang *et al*, Supplement to Hypertension, Vol. 19, No. 1, 01.01.1992, pp I-101 to I-109

   Claims 1 to 32, 35 and 36; somatostatin or an agonist thereof for decreasing body weight

5. None of the cited documents directly discloses that somatostatin or agonists thereof are useful in decreasing body weight.

6. Thus, the subject matter of Claims 1 to 32, 35 and 36 is new (Article 33(2) PCT).

7. With reference to lack of inventive step, however: Document D5 (WO-A-96/35950) discloses that "*ligands selective for somatostatin type-5 receptor ("SSTR-5") are effective in inhibiting release of amylin from pancreas cells*" (see page 2 lines 18 to 21 in D5) thus reducing hyperamylinemia. It is further indicated in document D5 (see page 1 lines 18 to 24) that *"The presence of an abnormally high concentration of amylin in the blood, i.e. hyperamylinemia, has been found in..//.. obese patients (see Huang et al., Hypertension 19 (Supp. I) :101 (1992)), ..Etc".* On turning to "*Huang et al*" (, *i.e.* document D7, see particularly page 107 therein) it is concluded therein that *"The present studies indicate that hyperamylinamia is not simply a passive partner to hyperinsulinemia. Rather, it could act as a causative mechanism of insulin resistance and associated metabolic derangements including obesity..Etc".* Hence, document D5 teaches that somatostatin type-5 receptor agonists reduce hyperamylinamia while document D7 teaches that hyperamylinamia plays a causative role in producing obesity. Thus, since the teachings of document D5 and D7 would clearly be considered together (since document D7 is cited in document D5), it is considered that the skilled man would be motivated to use somatostatin type-5 receptor agonists in the treatment of obesity in general. Hence, the subject matter of Claims 1 to 6, 8, 10 to 32, 35 and 36 lacks inventive step (Article 33(3) PCT).

8. With reference to the above points, it is acknowledged that the biochemical pathways responsible for obesity are complex and not fully elucidated. It is also noted however, that enough information concerning the functioning of these pathways was available before the priority date of the present application to enable the skilled man to predict with a reasonable degree of confidence that somatostatin-5 agonists would be useful in the treatment of obesity.

9. Furthermore, the present findings concerning lowering of plasma triglycerides in obese Zucker rats (see the present examples) appear to merely be a discovery relating to the mode of action of the obvious methods of present Claim 1.

10. None of the cited documents suggest or point towards the use of somatostatin type-2 selective receptor agonists for decreasing body weight in a patient. Hence, the subject matter of Claims 7 and 9 appears to be inventive (Article 33(3) PCT).

Claims 33, 34 and 37; compositions comprising somatostatin or an agonist thereof

11. Document D1 discloses pharmaceutical compositions (see page 6 line 34 to page 7 line 6 in D1) comprising somatostatin agonists such as *"H_2-c[-Cys-Phe-Phe-D-Trp-Lys Thr-Phe-Cys-NH_2"* (see page 6 lines 7 to 11 in D1 and compare with the compound of present Claim 33 and also the compound listed in present Claim 23 at page 32 line 5).

12. Similarly documents D5 and D6 (EP-A-0657174) disclose further pharmaceutical compositions comprising somatostatin or somatostatin agonists.

13. With reference to the comments set out in the preceding two paragraphs, it is noted that Claims 33, 34 and 37 are directed to pharmaceutical compositions *per SE* rather than methods of using said compositions.

14. Thus, the subject matter of Claims 33, 34 and 37 is not new in view of the disclosures of each of documents D1, D5 or D6 (Article 33(2) PCT).

SECTION VI

15. In view of the unavailability of the present priority documents it has not been possible for the IPEA to establish if the present claims are entitled to their earliest declared priority date. The present assessment of novelty and inventive step has been made on the assumption that the claims are entitled to their earliest declared priority date. The following documents (D3 and D4) may, however be considered to be relevant earlier applications in proceedings before certain authorities (see the states designated in respect of these earlier applications). Thus, it may be helpful to note that document D3 is potentially relevant to lack of novelty of Claims 1 to 10, 12 to 25, 27 to 37 while document D4 is potentially relevant to lack of novelty of Claims 1 to 10, 12 to 23, 27 to 37.

D3: WO-A-98/10786 published on 19.03.1998 filed on 10.09.1997 claiming priority from two previous applications filed on 12.09.96 and 10.10.96.

D4: WO-A-98/09991 published on 12.03.1998 filed on 04.09.1997 claiming priority

from a previous application filed on 05.09.1996.

SECTION VII

16. Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in documents D1 and D5 is not mentioned in the description, nor are these documents identified therein.

SECTION VIII

17. The further features of Claim 12 are repeatedly recited in Claims 13 to 22. Evidently, it would be possible to delete Claims 13 to 22 and make Claim 12 appendant to Claims 1 to 11. Thus, Claims 12 to 22 are considered to lack conciseness (Article 6 PCT). Similar considerations apply in respect of the further features of Claims 27 to 32

PATENT COOPERATION TREATY

09/423684

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

To:
DIBB LUPTON ALSOP
Attn. LUNT, Mark George Franc
Fountain Precinct
Balm Green
Sheffield S1 1RZ
UNITED KINGDOM

NOTIFICATION OF DECISION CONCERNING REQUEST FOR RECTIFICATION

(PCT Rule 91.1(f))

Applicant's or agent's file reference: P70920WO	Date of mailing (day/month/year): 05/11/1998
International application No.: PCT/EP 98/02999	REPLY DUE: NONE. However, see last paragraph below
Applicant: SOCIETE DE CONSEILS DE RECHERCHES ET D'A..et al.	International filing date (day/month/year): 13/05/1998

The applicant is hereby notified that this International Searching Authority has considered the request for rectification of obvious errors in the international application/in other papers submitted by the applicant to this Authority, and that it has decided:

1. [X] to authorise the rectification:

   [X] as requested by the applicant.

   [ ] to the extent set forth below*:

2. [ ] to refuse to authorise the rectification or part of it for the following reasons*:

A copy of this notification, together with a copy of the applicant's request for rectification, has been sent to the receiving Office and to the International Bureau.

* **If the authorisation of the rectification has been refused in whole or in part,** the applicant may request the International Bureau, before the technical preparations for international publication have been completed and subject to the payment of a fee, to publish the request for rectification together with the international application. See Rule 91.1(f), third and fourth sentences, and, for the amount of the fee, see Annex B2(WO), Volume I of the PCT Applicant's Guide.

Name and mailing address of the International Searching Authority	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Deborah Grandis

Form PCT/ISA/217 (July 1992)

****** RECORD COPY ******

DIBB LUPTON ALSOP

PATENT AND TRADE MARK ATTORNEYS

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Your ref

Our ref MGFL/SJC/P70920WO

7 October 1998

The European Patent Office
P B 5818
Patentlaan 2
2280 HV Rijswijk
The Netherlands

EPO - DG 1

12. 10. 1998

By Post and Fax: 00 31 70 340 3016

CONFIRMATION OF FAX

Dear Sirs

International Patent Application No PCT/EP98/02999
Societe de Conseils de Recherches et D'Applications Scientifiques, S.A. (S.C.R.A.S.) et al

A conversation with your Frau Durmann in the legal division of the European Patent Office in Munich has highlighted that the Powers of Attorney forwarded with my letters of 17 August 1998 and 21 August 1998 on behalf of the applicants in connection with the above-identified application are defective in that they appoint myself and my colleague Robert Hall "to act on applicant's behalf before the competent international authorities in connection with any and all international applications filed by the applicant with the United States Patent and Trademark Office as receiving office...". Since the above-identified application was filed with the European Patent Office as the receiving office, it follows that the Powers of Attorney would appear to be ineffective. This is purely a clerical error and is explained by the fact that we are acting on the instructions of US attorneys, who are themselves acting for a US corporation having a connection with the applicants. Accordingly, we were sent the Power of Attorney document normally used by our US associates who, like us and, at least initially, yourselves, overlooked the fact the form was inappropriate for applications for which the European Patent Office is the receiving office. Accordingly, new Powers of Attorney will have to be provided and this we are presently attending to. However, in the meantime, please confirm that you will permit us time within which to provide appropriate Powers of Attorney and for this purpose we suggest one month from the date of this letter.

Please confirm that this is acceptable.

rule 91 →

In perusing the file we note a number of typographical errors in the specification which have resulted from formatting errors when printing from our computers a document prepared in the United States. The problem is primarily only with Greek symbols used, namely α, β, γ, μ, $^\circ$ and $\pm$. Accordingly, please find enclosed in triplicate with the confirmation copy of this letter, new pages 3, 5, 6, 8, 10 to 17, 22 to 24 and 28 to 33, copies of the existing pages with the manuscript amendment being attached for your ease of reference.

DIBB LUPTON ALSOP

PATENT AND TRADE MARK ATTORNEYS

Continuation 2

Date 7 October 1998

It is believed that the amendments effected in these pages are self-evident and do not introduce any subject matter.

I attach copies of EPO Form 1037 and should be grateful if you would stamp one of these and return it to me immediately as an acknowledgement of receipt of this letter and enclosures.

Yours faithfully

Mark G F Lunt
European Patent Attorney

Enc (with confirmation copy only)

DIBB LUPTON ALSOP

PATENT AND TRADE MARK ATTORNEYS

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Direct Tel 0114 283 3492
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DX 708580 Sheffield 10

Your ref

Our ref MGFL/SJC/P70920WO

12 October 1998

The European Patent Office
P B 5818
Patentlaan 2
2280 HV Rijswijk
The Netherlands

R.91?

Dear Sirs

International Patent Application No PCT/EP98/02999
Societe de Conseils de Recherches et D'Applications Scientifiques, S.A. (S.C.R.A.S.) et al

Further to my letter dated 7 October 1998 in respect of the above-identified application, it has come to my attention that one of the replacement pages enclosed with that letter contained an error in that five lines of the description were lost in the re-formatting process. I enclose herewith a further replacement page 5. I should be grateful if you would use this to replace the page 5 enclosed with my earlier letter and apologise for any inconvenience caused.

I attach copies of EPO Form 1037 and should be grateful if you would stamp one of these and return it to me immediately as an acknowledgement of receipt of this letter and enclosure.

Yours faithfully

Mark G F Lunt
European Patent Attorney

Enc

and ultimately will be decided by the attending physician or veterinarian (e.g., between 5 µg/day to 5 mg/day). In one embodiment, the somatostatin agonist is administered to the patient until the patient has lost the requisite amount of body weight (e.g., the patient is no longer medically obese). In another embodiment, the somatostatin agonist is administered for the lifetime of the patient (e.g., maintaining normal body weight or secondary endpoints). In another embodiment, the somatostatin agonist is administered for cosmetic purposes.

The somatostatin agonist may be injected parenterally, e.g., intravenously, into the bloodstream of the subject being treated. However, it will be readily appreciated by those skilled in the art that the route, such as intravenous, subcutaneous, intramuscular, intraperitoneal, enterally, transdermally, transmucously, sustained released polymer compositions (e.g., a lactic acid polymer or copolymer microparticle or implant), profusion, nasal, oral, etc., will vary with the condition being treated and the activity and bioavailability of the somatostatin agonist being used.

While it is possible for the somatostatin agonist to be administered as the pure or substantially pure compound, it may also be presented as a pharmaceutical formulation or preparation. The formulations to be used in the present invention, for both humans and animals, comprise any of the somatostatin agonists to be described below, together with one or more pharmaceutically

Formulations suitable for parenteral (e.g., intravenous) administration, on the other hand, conveniently comprise sterile aqueous solutions of the active ingredient(s). Preferably, the solutions are isotonic with the blood of the subject to be treated. Such formulations may be conveniently prepared by dissolving solid active ingredient(s) in water to produce an aqueous solution, and rendering said solution sterile. The formulation may be presented in unit or multi-dose containers, for example, sealed ampoules or vials.

Formulations suitable for sustained release parenteral administrations (e.g., biodegradable polymer formulations such as polyesters containing lactic or glycolic acid residues) are also well known in the art. See, e.g., U.S. Patent Nos. 3,773,919 and 4,767,628 and PCT Publication No. WO 94/15587.

The somatostatin or somatostatin agonist may also be administered with other antiobesity agents such as phentermine, diethylpropion, methamphetamine, phendimetrazine, phenmetrazine, diethylpropion, phentermine, mazindol, dextroamphetamine, phentermine, bezphetamine, orlistat, β3-adrenergic agonists (e.g., BTA-234 and SR58611A), sibutramine, henylpropanolamine, dexfenturamine, leptin, or bromocriptine.

Other features and advantages of the invention will be apparent from the following description of the preferred embodiments and from the claims.

Abbreviations

β-Nal = β-naphthylalanine

β-Pal = β-pyridylalanine

hArg(Bu) = N-guanidino-(butyl)-homoarginine

$hArg(Et)_2$ = N, N'-guanidino-(dimethyl)-homoarginine

$hArg(CH_2CF_3)_2$ = N, N'-guanidino-bis-(2,2,2,-trifluoroethyl) - homoarginine

$hArg(CH_3$, hexyl) = N, N'-guanidino-(methyl, hexyl) - homoarginine

Lys(Me) = N-methyllysine

Lys(iPr) = N-isopropyllysine

AmPhe = aminomethylphenylalanine

AChxAla = aminocyclohexylalanine

Abu = α-aminobutyric acid

Tpo = 4-thiaproline

MeLeu = N-methylleucine

Orn = ornithine

Nle = norleucine

Nva = norvaline

Trp(Br) = 5-bromo-tryptophan

Trp(F) = 5-fluoro-tryptophan

$Trp(NO_2)$ = 5-nitro-tryptophan

Gaba = γ-aminobutyric acid

Bmp = β-mercaptopropionyl

Ac = acetyl

Pen = pencillamine

DETAILED DESCRIPTION OF THE INVENTION

It is believed that one skilled in the art can, based on the description herein, utilize the present

agonist, SSTR-2 agonist, SSTR-3 agonist, SSTR-4 agonist or an SSTR-5 agonist. In one embodiment, the somatostatin agonist of the present invention is an SSTR-5 agonist or an SSTR-2 agonist. What is meant by an "SSTR-5 agonist" or an "SSTR-2 agonist" is a compound which (1) has a high affinity (e.g., Ki of less than 1 μM or, preferably, of less than 10 nM, or less than 2 nM, or of less than 1 nM) for the SSTR-5 or SSTR-2, respectively (e.g., as defined by the receptor binding assay described below), and (2) decreases body weight of a patient (e.g., as defined by the biological assay described below). The somatostatin agonist may also be selective for a particular somatostatin receptor, e.g., have a higher binding affinity for a particular somatostatin receptor subtype as compared to the other receptor subtypes. In one embodiment, the somatostatin receptor is an SSTR-5 selective agonist or SSTR-2 selective agonist. What is meant by an SSTR-5 selective agonist is a somatostatin agonist which (1) has a higher binding affinity (i.e., Ki) for SSTR-5 than for either SSTR-1, SSTR-2, SSTR-3, or SSTR-4 and (2) decreases body weight of a patient (e.g., as defined by the biological assay described below). In one embodiment, the SSTR-5 selective agonist has a Ki for SSTR-5 that is at least 2 times (e.g., at least 5 times or at least 10 times) less than its Ki for the SSTR-2 receptor (e.g., as defined by the receptor binding assay described below).

Somatostatin agonists which can be used to practice the therapeutic method of the present invention include, but are not limited to, those covered by

U.S. Patent No. 4,310,518 (1982);
U.S. Patent No. 4,291,022 (1981);
U.S. Patent No. 4,238,481 (1980);
U.S. Patent No. 4,235,886 (1980);
U.S. Patent No. 4,224,190 (1980);
U.S. Patent No. 4,211,693 (1980);
U.S. Patent No. 4,190,648 (1980);
U.S. Patent No. 4,146,612 (1979);
U.S. Patent No. 4,133,782 (1979);
U.S. Patent No. 5,506,339 (1996);
U.S. Patent No. 4,261,885 (1981);
U.S. Patent No. 4,728,638 (1988);
U.S. Patent No. 4,282,143 (1981);
U.S. Patent No. 4,215,039 (1980);
U.S. Patent No. 4,209,426 (1980);
U.S. Patent No. 4,190,575 (1980);
EP Patent No. 0 389 180 (1990);
EP Application No. 0 505 680 (1982);
EP Application No. 0 083 305 (1982);
EP Application No. 0 030 920 (1980);
PCT Application No. WO 88/05052 (1988);
PCT Application No. WO 90/12811 (1990);
PCT Application No. WO 97/01579 (1997);
PCT Application No. WO 91/18016 (1991);
U.K. Application No. GB 2,095,261 (1981); and
French Application No. FR 2,522,655 (1983).

Examples of somatostatin agonists include, but are not limited to, the following somatostatin analogs which are disclosed in the above-cited references:

H-D-β-Nal-Cys-Tyr-D-Trp-Lys-Thr-Cys-Thr-NH_2 (BIM-23014);

H-D-Phe-Cys-Phe-D-Trp-Lys-Thr-Cys-β-Nal-NH_2;

H-D-Phe-Cys-Tyr-D-Trp-Lys-Thr-Cys-β-Nal-NH_2;

H-D-β-Nal-Cys-Phe-D-Trp-Lys-Thr-Cys-Thr-NH_2;

H-D-Phe-Cys-Tyr-D-Trp-Lys-Thr-Pen-Thr-NH_2;

H-D-Phe-Cys-Phe-D-Trp-Lys-Thr-Pen-Thr-NH_2;

H-D-Phe-Cys-Tyr-D-Trp-Lys-Thr-Pen-Thr-OH;

H-D-Phe-Cys-Phe-D-Trp-Lys-Thr-Pen-Thr-OH;

H-Gly-Pen-Phe-D-Trp-Lys-Thr-Cys-Thr-OH;

H-Phe-Pen-Tyr-D-Trp-Lys-Thr-Cys-Thr-OH;

H-Phe-Pen-Phe-D-Trp-Lys-Thr-Pen-Thr-OH;

H-D-Phe-Cys-Phe-D-Trp-Lys-Thr-Cys-Thr-ol (Octreotide);

H-D-Phe-Cys-Phe-D-Trp-Lys-Thr-Cys-Thr-NH_2;

H-D-Trp-Cys-Tyr-D-Trp-Lys-Val-Cys-Thr-NH_2;

H-D-Trp-Cys-Phe-D-Trp-Lys-Thr-Cys-Thr-NH_2;

H-D-Phe-Cys-Tyr-D-Trp-Lys-Val-Cys-Thr-NH_2;

H-D-Phe-Cys-Tyr-D-Trp-Lys-Val-Cys-Trp-NH_2;

H-D-Phe-Cys-Tyr-D-Trp-Lys-Val-Cys-Thr-NH_2;

Ac-D-Phe-Lys*-Tyr-D-Trp-Lys-Val-Asp-Thr-NH_2 (an amide bridge formed between Lys* and Asp);

Ac-hArg$(Et)_2$-Gly-Cys-Phe-D-Trp-Lys-Thr-Cys-Thr-NH_2;

Ac-D-hArg$(Et)_2$-Gly-Cys-Phe-D-Trp-Lys-Thr-Cys-Thr-NH_2;

Ac-D-hArg(Bu)-Gly-Cys-Phe-D-Trp-Lys-Thr-Cys-Thr-NH_2;

Ac-D-hArg$(Et)_2$-Cys-Phe-D-Trp-Lys-Thr-Cys-Thr-NH_2;

Ac-L-hArg$(Et)_2$-Cys-Phe-D-Trp-Lys-Thr-Cys-Thr-NH_2;

Ac-D-hArg$(CH_2CF_3)_2$-Cys-Phe-D-Trp-Lys-Thr-Cys-Thr-NH_2;

Ac-D-hArg$(CH_2CF_3)_2$-Gly-Cys-Phe-D-Trp-Lys-Thr-Cys-Thr-NH_2;

Ac-D-hArg$(CH_2CF_3)_2$-Gly-Cys-Phe-D-Trp-Lys-Thr-Cys-Phe-NH_2;

Ac-D-hArg$(CH_2CF_3)_2$-Gly-Cys-Phe-D-Trp-Lys-Thr-Cys-Thr-NHEt;

Ac-L-hArg(CH_2-CF_3)$_2$-Gly-Cys-Phe-D-Trp-Lys-Thr-Cys-Thr-NH_2;

Ac-D-hArg(CH_2CF_3)$_2$-Gly-Cys-Phe-D-Trp-Lys(Me)-Thr-Cys-Thr-NH_2;

Ac-D-hArg(CH_2CF_3)$_2$-Gly-Cys-Phe-D-Trp-Lys(Me)-Thr-Cys-Thr-NHEt;

Ac-hArg(CH_3, hexyl)-Gly-Cys-Phe-D-Trp-Lys-Thr-Cys-Thr-NH_2;

H-hArg(hexyl$_2$)-Gly-Cys-Phe-D-Trp-Lys-Thr-Cys-Thr-NH_2;

Ac-D-hArg(Et)$_2$-Gly-Cys-Phe-D-Trp-Lys-Thr-Cys-Thr-NHEt;

Ac-D-hArg(Et)$_2$-Gly-Cys-Phe-D-Trp-Lys-Thr-Cys-Phe-NH_2;

Propionyl-D-hArg(Et)$_2$-Gly-Cys-Phe-D-Trp-Lys(iPr)-Thr-Cys-Thr-NH_2;

Ac-D-β-Nal-Gly-Cys-Phe-D-Trp-Lys-Thr-Cys-Gly-hArg(Et)$_2$-NH_2;

Ac-D-Lys(iPr)-Gly-Cys-Phe-D-Trp-Lys-Thr-Cys-Thr-NH_2;

Ac-D-hArg(CH_2CF_3)$_2$-D-hArg(CH_2CF_3)$_2$-Gly-Cys-Phe-D-Trp-Lys-Thr-Cys-Thr-NH_2;

Ac-D-hArg(CH_2CF_3)$_2$-D-hArg(CH_2CF_3)$_2$-Gly-Cys-Phe-D-Trp-Lys-Thr-Cys-Phe-NH_2;

Ac-D-hArg(Et)$_2$-D-hArg(Et)$_2$-Gly-Cys-Phe-D-Trp-Lys-Thr-Cys-Thr-NH_2;

Ac-Cys-Lys-Asn-4-Cl-Phe-Phe-D-Trp-Lys-Thr-Phe-Thr-Ser-D-Cys-NH_2;

H-Bmp-Tyr-D-Trp-Lys-Val-Cys-Thr-NH_2;

H-Bmp-Tyr-D-Trp-Lys-Val-Cys-Phe-NH_2;

H-Bmp-Tyr-D-Trp-Lys-Val-Cys-p-Cl-Phe-NH_2;

H-Bmp-Tyr-D-Trp-Lys-Val-Cys-β-Nal-NH_2;

H-D-β-Nal-Cys-Tyr-D-Trp-Lys-Val-Cys-Thr-NH_2;

H-D-Phe-Cys-Tyr-D-Trp-Lys-Abu-Cys-Thr-NH_2;

H-D-Phe-Cys-Tyr-D-Trp-Lys-Abu-Cys-β-Nal-NH_2;

H-pentafluoro-D-Phe-Cys-Tyr-D-Trp-Lys-Val-Cys-Thr-NH_2;

Ac-D-β-Nal-Cys-pentafluoro-Phe-D-Trp-Lys-Val-Cys-Thr-NH_2;

H-D-β-Nal-Cys-Tyr-D-Trp-Lys-Val-Cys-β-Nal-NH_2;

H-D-Phe-Cys-Tyr-D-Trp-Lys-Val-Cys-β-Nal-NH_2;

H-D-β-Nal-Cys-Tyr-D-Trp-Lys-Abu-Cys-Thr-NH_2;

H-D-p-Cl-Phe-Cys-Tyr-D-Trp-Lys-Abu-Cys-Thr-NH_2;

Ac-D-p-Cl-Phe-Cys-Tyr-D-Trp-Lys-Abu-Cys-Thr-NH_2;

H-D-Phe-Cys-β-Nal-D-Trp-Lys-Val-Cys-Thr-NH_2;

H-D-Phe-Cys-Tyr-D-Trp-Lys-Cys-Thr-NH_2;

cyclo(Pro-Phe-D-Trp-N-Me-Lys-Thr-Phe);

cyclo(Pro-Phe-D-Trp-N-Me-Lys-Thr-Phe);

cyclo(Pro-Phe-D-Trp-Lys-Thr-N-Me-Phe);

cyclo(N-Me-Ala-Tyr-D-Trp-Lys-Thr-Phe);

cyclo(Pro-Tyr-D-Trp-Lys-Thr-Phe);

cyclo(Pro-Phe-D-Trp-Lys-Thr-Phe);

cyclo(Pro-Phe-L-Trp-Lys-Thr-Phe);

cyclo(Pro-Phe-D-Trp(F)-Lys-Thr-Phe);

cyclo(Pro-Phe-Trp(F)-Lys-Thr-Phe);

cyclo(Pro-Phe-D-Trp-Lys-Ser-Phe);

cyclo(Pro-Phe-D-Trp-Lys-Thr-p-Cl-Phe);

cyclo(D-Ala-N-Me-D-Phe-D-Thr-D-Lys-Trp-D-Phe);

cyclo(D-Ala-N-Me-D-Phe-D-Val-Lys-D-Trp-D-Phe);

cyclo(D-Ala-N-Me-D-Phe-D-Thr-Lys-D-Trp-D-Phe);

cyclo(D-Abu-N-Me-D-Phe-D-Val-Lys-D-Trp-D-Tyr);

cyclo(Pro-Tyr-D-Trp-t-4-AchxAla-Thr-Phe);

cyclo(Pro-Phe-D-Trp-t-4-AchxAla-Thr-Phe);

cyclo(N-Me-Ala-Tyr-D-Trp-Lys-Val-Phe);

cyclo(N-Me-Ala-Tyr-D-Trp-t-4-AchxAla-Thr-Phe);

cyclo(Pro-Tyr-D-Trp-4-Amphe-Thr-Phe);

cyclo(Pro-Phe-D-Trp-4-Amphe-Thr-Phe);

cyclo(N-Me-Ala-Tyr-D-Trp-4-Amphe-Thr-Phe);

cyclo(Asn-Phe-Phe-D-Trp-Lys-Thr-Phe-Gaba);

cyclo(Asn-Phe-Phe-D-Trp-Lys-Thr-Phe-Gaba-Gaba);

cyclo(Asn-Phe-D-Trp-Lys-Thr-Phe);

cyclo(Asn-Phe-Phe-D-Trp-Lys-Thr-Phe-$NH(CH_2)_4CO$);

cyclo(Asn-Phe-Phe-D-Trp-Lys-Thr-Phe-β-Ala);

cyclo(Asn-Phe-Phe-D-Trp-Lys-Thr-Phe-D-Glu)-OH;

cyclo(Phe-Phe-D-Trp-Lys-Thr-Phe);

cyclo(Phe-Phe-D-Trp-Lys-Thr-Phe-Gly);

cyclo(Phe-Phe-D-Trp-Lys-Thr-Phe-Gaba);

cyclo(Asn-Phe-Phe-D-Trp-Lys-Thr-Phe-Gly);

cyclo(Asn-Phe-Phe-D-Trp(F)-Lys-Thr-Phe-Gaba);

cyclo(Asn-Phe-Phe-D-Trp(NO_2)-Lys-Thr-Phe-Gaba);

cyclo(Asn-Phe-Phe-Trp(Br)-Lys-Thr-Phe-Gaba);

cyclo(Asn-Phe-Phe-D-Trp-Lys-Thr-Phe(I)-Gaba);

cyclo(Asn-Phe-Phe-D-Trp-Lys-Thr-Tyr(But)-Gaba);

cyclo(Bmp-Lys-Asn-Phe-Phe-D-Trp-Lys-Thr-Phe-Thr-Pro-Cys)-OH;

cyclo(Bmp-Lys-Asn-Phe-Phe-D-Trp-Lys-Thr-Phe-Thr-Pro-Cys)-OH;

cyclo(Bmp-Lys-Asn-Phe-Phe-D-Trp-Lys-Thr-Phe-Thr-Tpo-Cys)-OH;

cyclo(Bmp-Lys-Asn-Phe-Phe-D-Trp-Lys-Thr-Phe-Thr-MeLeu-Cys)-OH;

cyclo(Phe-Phe-D-Trp-Lys-Thr-Phe-Phe-Gaba);

cyclo(Phe-Phe-D-Trp-Lys-Thr-Phe-D-Phe-Gaba);

cyclo(Phe-Phe-D-Trp(5F)-Lys-Thr-Phe-Phe-Gaba);

cyclo(Asn-Phe-Phe-D-Trp-Lys(Ac)-Thr-Phe-NH-$(CH_2)_3$-CO);

cyclo(Lys-Phe-Phe-D-Trp-Lys-Thr-Phe-Gaba);

cyclo(Lys-Phe-Phe-D-Trp-Lys-Thr-Phe-Gaba);

cyclo(Orn-Phe-Phe-D-Trp-Lys-Thr-Phe-Gaba);

H-Cys-Phe-Phe-D-Trp-Lys-Thr-Phe-Cys-NH_2 (BIM-23268);

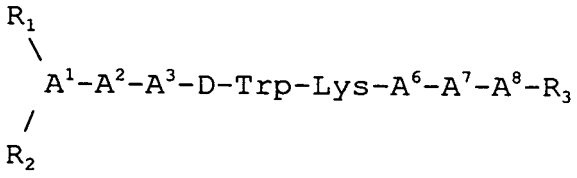
H-Cys-Phe-Phe-D-Trp-Lys-Ser-Phe-Cys-NH_2 (BIM-23284);

H-Cys-Phe-Tyr-D-Trp-Lys-Thr-Phe-Cys-NH_2 (BIM-23295); and

H-Cys-Phe-Tyr(I)-D-Trp-Lys-Thr-Phe-Cys-NH_2 (BIM-23313).

Note that for all somatostatin agonists described herein, each amino acid residue represents the structure of -NH-C(R)H-CO-, in which R is the side chain (e.g., CH_3 for Ala) except for Thr-ol which means -NH-CH(CH(CH_3)OH)-CH_2-OH and Pro which means prolinyl. Lines between amino acid residues represent peptide bonds which join the amino acids. Also, where the amino acid residue is optically active, it is the L-form configuration that is intended unless D-form is expressly designated. A disulfide bridge is formed between the two free thiols (e.g., Cys, Pen, or Bmp residues); however, it is not shown.

Use of linear somatostatin agonists of the following formula is also within the invention:



wherein

A^1 is a D- or L- isomer of Ala, Leu, Ile, Val, Nle, Thr, Ser, β-Nal, β-Pal, Trp, Phe, 2,4-dichloro-Phe, pentafluoro-Phe, p-X-Phe, or o-X-Phe, wherein X is CH_3, Cl, Br, F, OH, OCH_3 or NO_2;

A^2 is Ala, Leu, Ile, Val, Nle, Phe, β-Nal, pyridyl-Ala, Trp, 2,4-dichloro-Phe, pentafluoro-Phe, o-X-Phe, or p-X-Phe, wherein X is CH_3, Cl, Br, F, OH, OCH_3 or NO_2;

A^3 is pyridyl-Ala, Trp, Phe, β-Nal, 2,4-dichloro-Phe, pentafluoro-Phe, o-X-Phe, or p-X-Phe, wherein X is CH_3, Cl, Br, F, OH, OCH_3 or NO_2;

A^6 is Val, Ala, Leu, Ile, Nle, Thr, Abu, or Ser;

A^7 is Ala, Leu, Ile, Val, Nle, Phe, β-Nal, pyridyl-Ala, Trp, 2,4-dichloro-Phe, pentafluoro-Phe, o-X-Phe, or p-X-Phe, wherein X is CH_3, Cl, Br, F, OH, OCH_3 or NO_2;

A^8 is a D- or L-isomer of Ala, Leu, Ile, Val, Nle, Thr, Ser, Phe, β-Nal, pyridyl-Ala, Trp, 2,4-dichloro-Phe, pentafluoro-Phe, p-X-Phe, or o-X-Phe, wherein X is CH_3, Cl, Br, F, OH, OCH_3 or NO_2;

each R_1 and R_2, independently, is H, lower acyl or lower alkyl; and R_3 is OH or NH_2; provided that at least one of A^1 and A^8 and one of A^2 and A^7 must be an aromatic amino acid; and further provided that A^1, A^2, A^7 and A^8 cannot all be aromatic amino acids.

Examples of linear agonists to be used in the method of this invention include:

H-D-Phe-p-chloro-Phe-Tyr-D-Trp-Lys-Thr-Phe-Thr-NH_2;

H-D-Phe-p-NO_2-Phe-Tyr-D-Trp-Lys-Val-Phe-Thr-NH_2;

H-D-Nal-p-chloro-Phe-Tyr-D-Trp-Lys-Val-Phe-Thr-NH_2;

H-D-Phe-Phe-Phe-D-Trp-Lys-Thr-Phe-Thr-NH_2 (BIM-23052);

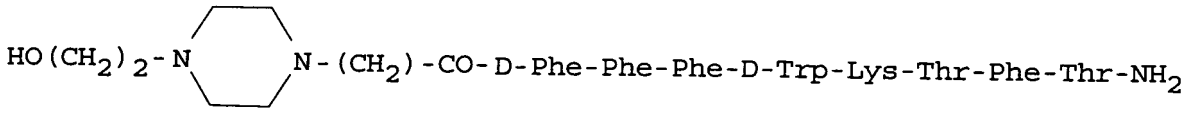
H-D-Phe-Phe-Tyr-D-Trp-Lys-Val-Phe-Thr-NH_2;

H-D-Phe-p-chloro-Phe-Tyr-D-Trp-Lys-Val-Phe-Thr-NH_2;

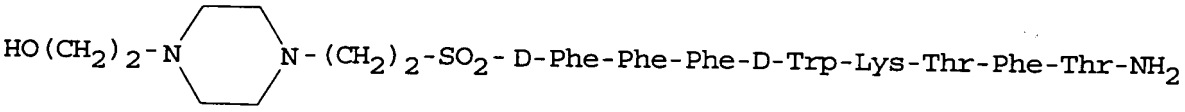
and

H-D-Phe-Ala-Tyr-D-Trp-Lys-Val-Ala-β-D-Nal-NH_2.

If desired, one or more chemical moieties, e.g., a sugar derivative, mono or poly-hydroxy C_{2-12} alkyl, mono or poly-hydroxy C_{2-12} acyl groups, or a piperazine derivative, can be attached to the somatostatin agonist, e.g., to the N-terminus amino acid. See PCT Application WO 88/02756, European Application 0 329 295, and PCT Application No. WO 94/04752. An example of a somatostatin agonists which contain N-terminal chemical substitutions are:



(BIM-23272);



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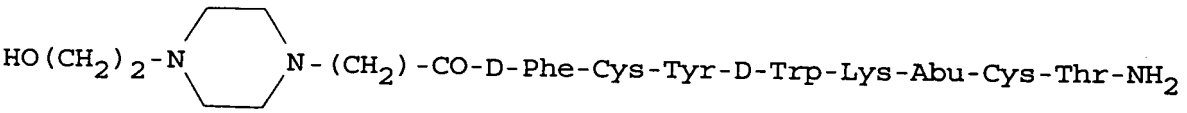
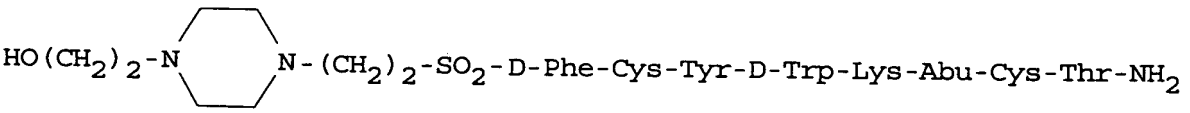


(BIM-23190); and



(BIM-23197).

Synthesis of somatostatin agonists

The methods for synthesizing somatostatin agonists is well documented and are within the ability of a person of ordinary skill in the art.

Weight Loss Studies

The effect of chronic (6 day) treatment with BIM-23268 on body weight gain/loss was examined in an obese animal model, the fatty (fa/fa) Zucker rats (purchased from Harlan-Olac, Bicester, Oxon, U.K. See Bray, G., Federation Proceedings 36:148-153 (1977). Eleven male fatty Zucker rats weighing about 450 grams were randomly divided into two groups, and their initial body weights recorded. The animals were housed in pairs in a normal 12 hour light:12 hour darkness cycle at 20 ± 2°C and fed overnight *ad libitum*.

For the group assigned to receive drug treatment, the rats received the type-5 somatostatin receptor selective agonist BIM-23268C at 3 mg/kg, by subcutaneous injection twice a day at 10:00 a.m. and 5:00 p.m. The other group was treated with a subcutaneous injection of 0.1 ml/100 g of saline twice a day at 10:00 a.m. and 5:00 p.m. The animals were subjected to the BIM-23268 or saline treatment for a total of six days.

At 10:00 a.m. each day, food was removed and replaced with accurately weight 100 gram food pellet (a standard laboratory rat diet, Beekay rat and mouse diet, Bantin & Kingman, Hull, Humberside, U.K.). The amount of food remaining a 10:00 a.m. the next day was accurately weighed, recorded and replaced with 100 grams of fresh food pellets.

The animals were weighed each day during the 6-day treatment period at 5:00 p.m. The untreated control group mean weight was 414.09 at the start of the trial

(Traysylol, Bayer UK, Hayward's Health, W. Sussex, U.K.) and heparin (Sigma Chemical Co., Poole, Dorset, U.K.) were added to the blood samples to a final concentration of 400 KIU/ml and 100 units/ml, respectively. Plasma fractions were prepared from these samples by centrifugation at 4000 x G in a microfuge, for the estimation of triglycerides and glycerol. Samples were then stored at -80°C until assayed.

Plasma glycerol and triglycerides were determined using the Sigma Enzymatic (Tinder) calorimetric assay kit (Cat #337-B, Sigma Chemical Co., Poole, Dorset, U.K.) and measuring absorbance at 540 nm in a spectrophotometer.

After six days of treatment with BIM-23268C at 3 mg/kg twice a day by subcutaneous injection, both plasma glycerol and triglycerides were significantly lowered, as exemplified by the samples taken at tim 30 and 60 minutes before the oral glucose challenge. See Fig. 1 and Fig. 2. The administration of an oral glucose challenge have no significant effect on plasma lipids. The BIM-23628C treated group showed a significantly lower plasma glycerol and triglycerides throughout the 2-hour test period. The results suggested that BIM-23268C, following a 6-day treatment period at the prescribed dose was effective in reducing hypertriglyceridemia.

Assessment of Efficacy in Patient

The effect of the somatostatin agonist on obesity can be examined in patients by assessing total body weight, body mass index, total adipose tissue content, subcutaneous tissue content, visceral adipose tissue

and was 418.89 after six days. The BIM-23268 treated group's mean weight was 413.6 at the start of the trial and remained at 413.6 after six days. The average food consumption for the control group was 26.0 g/rat/day and for the BIM-26268 group was 25.9 g/rat/day.

These results showed that body weight gain was lower in animals treated with BIM-23268. The effect on body weight change was not due to a toxic effect of the agent, as the treated group appeared healthy, and there was no difference in the amount of food consumed over the entire treatment period.

Secondary Endpoints of Efficacy

Because of the amount of weight that must be lost to achieve a clinically important alteration in risk for various sequelae of obesity, the Food and Drug Administration guidelines for the evaluation of weight-control drugs have recommended that additional endpoints showing a decrease in risk factors such as lipemia be monitored.

Obese (fa/fa) Zucker rats were treated as in example 1 above. On the last day of treatment (day 6), food was removed at 5:00 p.m., and the rats were fasted overnight. At 9:00 a.m. the next day, the animals were subjected to a glucose challenge, given as 0.8 gram/kg of glucose orally. Periodic 400 µl of blood samples were taken from the tail vein (Peterson, R.G., ILAR News, 32:16-19 (1990)) 60 min. and 30 min. before and at 30, 60, 90, and 120 min. after the administration of the glucose challenge (0.8 gram/kg orally). Aprotinin

22. A method of claim 11, wherein said patient is an non-insulin-dependent diabetic human.

23. A method according to claim 1 wherein the somatostatin agonist is

H-D-β-Nal-Cys-Tyr-D-Trp-Lys-Thr-Cys-Thr-NH_2,

H-D-Phe-Cys-Phe-D-Trp-Lys-Thr-Cys-β-Nal-NH_2,

H-D-Phe-Cys-Tyr-D-Trp-Lys-Thr-Cys-β-Nal-NH_2,

H-D-β-Nal-Cys-Phe-D-Trp-Lys-Thr-Cys-Thr-NH_2,

H-D-Phe-Cys-Tyr-D-Trp-Lys-Thr-Pen-Thr-NH_2,

H-D-Phe-Cys-Phe-D-Trp-Lys-Thr-Pen-Thr-NH_2,

H-D-Phe-Cys-Tyr-D-Trp-Lys-Thr-Pen-Thr-OH,

H-D-Phe-Cys-Phe-D-Trp-Lys-Thr-Pen-Thr-OH,

H-Gly-Pen-Phe-D-Trp-Lys-Thr-Cys-Thr-OH,

H-Phe-Pen-Tyr-D-Trp-Lys-Thr-Cys-Thr-OH,

H-Phe-Pen-Phe-D-Trp-Lys-Thr-Pen-Thr-OH,

H-D-Phe-Cys-Phe-D-Trp-Lys-Thr-Cys-Thr-ol

H-D-Phe-Cys-Phe-D-Trp-Lys-Thr-Cys-Thr-NH_2,

H-D-Trp-Cys-Tyr-D-Trp-Lys-Val-Cys-Thr-NH_2,

H-D-Trp-Cys-Phe-D-Trp-Lys-Thr-Cys-Thr-NH_2,

H-D-Phe-Cys-Tyr-D-Trp-Lys-Val-Cys-Thr-NH_2,

H-D-Phe-Cys-Tyr-D-Trp-Lys-Val-Cys-Trp-NH_2,

H-D-Phe-Cys-Tyr-D-Trp-Lys-Val-Cys-Thr-NH_2,

Ac-D-Phe-Lys^*-Tyr-D-Trp-Lys-Val-Asp-Thr-NH_2 (an amide bridge formed between Lys^* and Asp),

Ac-hArg(Et)$_2$-Gly-Cys-Phe-D-Trp-Lys-Thr-Cys-Thr-NH_2,

Ac-D-hArg(Et)$_2$-Gly-Cys-Phe-D-Trp-Lys-Thr-Cys-Thr-NH_2,

Ac-D-hArg(Bu)-Gly-Cys-Phe-D-Trp-Lys-Thr-Cys-Thr-NH_2,

Ac-D-hArg(Et)$_2$-Cys-Phe-D-Trp-Lys-Thr-Cys-Thr-NH_2,

Ac-L-hArg(Et)$_2$-Cys-Phe-D-Trp-Lys-Thr-Cys-Thr-NH_2,

Ac-D-hArg(CH_2CF_3)$_2$-Cys-Phe-D-Trp-Lys-Thr-Cys-Thr-NH_2,

Ac-D-hArg(CH_2CF_3)$_2$-Gly-Cys-Phe-D-Trp-Lys-Thr-Cys-Thr-NH_2,

Ac-D-hArg(CH_2CF_3)$_2$-Gly-Cys-Phe-D-Trp-Lys-Thr-Cys-Phe-NH_2,

Ac-D-hArg(CH_2CF_3)$_2$-Gly-Cys-Phe-D-Trp-Lys-Thr-Cys-Thr-NHEt,

Ac-L-hArg(CH_2-CF_3)$_2$-Gly-Cys-Phe-D-Trp-Lys-Thr-Cys-Thr-NH_2,

Ac-D-hArg(CH_2CF_3)$_2$-Gly-Cys-Phe-D-Trp-Lys(Me)-Thr-Cys-Thr-NH_2,

Ac-D-hArg(CH_2CF_3)$_2$-Gly-Cys-Phe-D-Trp-Lys(Me)-Thr-Cys-Thr-NHEt,

Ac-hArg(CH_3, hexyl)-Gly-Cys-Phe-D-Trp-Lys-Thr-Cys-Thr-NH_2,

H-hArg(hexyl$_2$)-Gly-Cys-Phe-D-Trp-Lys-Thr-Cys-Thr-NH_2,

Ac-D-hArg(Et)$_2$-Gly-Cys-Phe-D-Trp-Lys-Thr-Cys-Thr-NHEt,

Ac-D-hArg(Et)$_2$-Gly-Cys-Phe-D-Trp-Lys-Thr-Cys-Phe-NH_2,

Propionyl-D-hArg(Et)$_2$-Gly-Cys-Phe-D-Trp-Lys(iPr)-Thr-Cys-Thr-NH_2,

Ac-D-β-Nal-Gly-Cys-Phe-D-Trp-Lys-Thr-Cys-Gly-hArg(Et)$_2$-NH_2,

Ac-D-Lys(iPr)-Gly-Cys-Phe-D-Trp-Lys-Thr-Cys-Thr-NH_2,

Ac-D-hArg(CH_2CF_3)$_2$-D-hArg(CH_2CF_3)$_2$-Gly-Cys-Phe-D-Trp-Lys-Thr-Cys-Thr-NH_2,

Ac-D-hArg(CH_2CF_3)$_2$-D-hArg(CH_2CF_3)$_2$-Gly-Cys-Phe-D-Trp-Lys-Thr-Cys-Phe-NH_2,

Ac-D-hArg(Et)$_2$-D-hArg(Et)$_2$-Gly-Cys-Phe-D-Trp-Lys-Thr-Cys-Thr-NH_2,

Ac-Cys-Lys-Asn-4-Cl-Phe-Phe-D-Trp-Lys-Thr-Phe-Thr-Ser-D-Cys-NH_2,

H-Bmp-Tyr-D-Trp-Lys-Val-Cys-Thr-NH_2,

H-Bmp-Tyr-D-Trp-Lys-Val-Cys-Phe-NH_2,

H-Bmp-Tyr-D-Trp-Lys-Val-Cys-p-Cl-Phe-NH_2,

H-Bmp-Tyr-D-Trp-Lys-Val-Cys-β-Nal-NH_2,

H-D-β-Nal-Cys-Tyr-D-Trp-Lys-Val-Cys-Thr-NH_2,

H-D-Phe-Cys-Tyr-D-Trp-Lys-Abu-Cys-Thr-NH_2,

H-D-Phe-Cys-Tyr-D-Trp-Lys-Abu-Cys-β-Nal-NH_2,

H-pentafluoro-D-Phe-Cys-Tyr-D-Trp-Lys-Val-Cys-Thr-NH_2,

Ac-D-β-Nal-Cys-pentafluoro-Phe-D-Trp-Lys-Val-Cys-Thr-NH_2,

H-D-β-Nal-Cys-Tyr-D-Trp-Lys-Val-Cys-β-Nal-NH_2,

H-D-Phe-Cys-Tyr-D-Trp-Lys-Val-Cys-β-Nal-NH_2,

H-D-β-Nal-Cys-Tyr-D-Trp-Lys-Abu-Cys-Thr-NH_2,

H-D-p-Cl-Phe-Cys-Tyr-D-Trp-Lys-Abu-Cys-Thr-NH_2,

Ac-D-p-Cl-Phe-Cys-Tyr-D-Trp-Lys-Abu-Cys-Thr-NH_2,

H-D-Phe-Cys-β-Nal-D-Trp-Lys-Val-Cys-Thr-NH_2,

H-D-Phe-Cys-Tyr-D-Trp-Lys-Cys-Thr-NH_2,

cyclo(Pro-Phe-D-Trp-N-Me-Lys-Thr-Phe),

cyclo(Pro-Phe-D-Trp-N-Me-Lys-Thr-Phe),

cyclo(Pro-Phe-D-Trp-Lys-Thr-N-Me-Phe),

cyclo(N-Me-Ala-Tyr-D-Trp-Lys-Thr-Phe),

cyclo(Pro-Tyr-D-Trp-Lys-Thr-Phe),

cyclo(Pro-Phe-D-Trp-Lys-Thr-Phe),

cyclo(Pro-Phe-L-Trp-Lys-Thr-Phe),

cyclo(Pro-Phe-D-Trp(F)-Lys-Thr-Phe),

cyclo(Pro-Phe-Trp(F)-Lys-Thr-Phe),

cyclo(Pro-Phe-D-Trp-Lys-Ser-Phe),

cyclo(Pro-Phe-D-Trp-Lys-Thr-p-Cl-Phe),

cyclo(D-Ala-N-Me-D-Phe-D-Thr-D-Lys-Trp-D-Phe),

cyclo(D-Ala-N-Me-D-Phe-D-Val-Lys-D-Trp-D-Phe),

cyclo(D-Ala-N-Me-D-Phe-D-Thr-Lys-D-Trp-D-Phe),

cyclo(D-Abu-N-Me-D-Phe-D-Val-Lys-D-Trp-D-Tyr),

cyclo(Pro-Tyr-D-Trp-t-4-AchxAla-Thr-Phe),

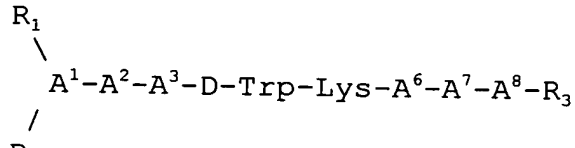
cyclo(Pro-Phe-D-Trp-t-4-AchxAla-Thr-Phe),

cyclo(N-Me-Ala-Tyr-D-Trp-Lys-Val-Phe),

cyclo(N-Me-Ala-Tyr-D-Trp-t-4-AchxAla-Thr-Phe),
cyclo(Pro-Tyr-D-Trp-4-Amphe-Thr-Phe),
cyclo(Pro-Phe-D-Trp-4-Amphe-Thr-Phe),
cyclo(N-Me-Ala-Tyr-D-Trp-4-Amphe-Thr-Phe),
cyclo(Asn-Phe-Phe-D-Trp-Lys-Thr-Phe-Gaba),
cyclo(Asn-Phe-Phe-D-Trp-Lys-Thr-Phe-Gaba-Gaba),
cyclo(Asn-Phe-D-Trp-Lys-Thr-Phe),
cyclo(Asn-Phe-Phe-D-Trp-Lys-Thr-Phe-$NH(CH_2)_4CO$),
cyclo(Asn-Phe-Phe-D-Trp-Lys-Thr-Phe-β-Ala),
cyclo(Asn-Phe-Phe-D-Trp-Lys-Thr-Phe-D-Glu)-OH,
cyclo(Phe-Phe-D-Trp-Lys-Thr-Phe),
cyclo(Phe-Phe-D-Trp-Lys-Thr-Phe-Gly),
cyclo(Phe-Phe-D-Trp-Lys-Thr-Phe-Gaba),
cyclo(Asn-Phe-Phe-D-Trp-Lys-Thr-Phe-Gly),
cyclo(Asn-Phe-Phe-D-Trp(F)-Lys-Thr-Phe-Gaba),
cyclo(Asn-Phe-Phe-D-Trp(NO_2)-Lys-Thr-Phe-Gaba),
cyclo(Asn-Phe-Phe-Trp(Br)-Lys-Thr-Phe-Gaba),
cyclo(Asn-Phe-Phe-D-Trp-Lys-Thr-Phe(I)-Gaba),
cyclo(Asn-Phe-Phe-D-Trp-Lys-Thr-Tyr(But)-Gaba),
cyclo(Bmp-Lys-Asn-Phe-Phe-D-Trp-Lys-Thr-Phe-Thr-Pro-Cys)-OH,
cyclo(Bmp-Lys-Asn-Phe-Phe-D-Trp-Lys-Thr-Phe-Thr-Pro-Cys)-OH,
cyclo(Bmp-Lys-Asn-Phe-Phe-D-Trp-Lys-Thr-Phe-Thr-Tpo-Cys)-OH,
cyclo(Bmp-Lys-Asn-Phe-Phe-D-Trp-Lys-Thr-Phe-Thr-MeLeu-Cys)-OH,
cyclo(Phe-Phe-D-Trp-Lys-Thr-Phe-Phe-Gaba),
cyclo(Phe-Phe-D-Trp-Lys-Thr-Phe-D-Phe-Gaba),
cyclo(Phe-Phe-D-Trp(5F)-Lys-Thr-Phe-Phe-Gaba),

cyclo(Asn-Phe-Phe-D-Trp-Lys(Ac)-Thr-Phe-NH-$(CH_2)_3$-CO),
cyclo(Lys-Phe-Phe-D-Trp-Lys-Thr-Phe-Gaba),
cyclo(Lys-Phe-Phe-D-Trp-Lys-Thr-Phe-Gaba),
cyclo(Orn-Phe-Phe-D-Trp-Lys-Thr-Phe-Gaba),
H-Cys-Phe-Phe-D-Trp-Lys-Thr-Phe-Cys-NH_2 ,
H-Cys-Phe-Phe-D-Trp-Lys-Ser-Phe-Cys-NH_2 ,
H-Cys-Phe-Tyr-D-Trp-Lys-Thr-Phe-Cys-NH_2 or
H-Cys-Phe-Tyr(I)-D-Trp-Lys-Thr-Phe-Cys-NH_2 .

24. A method according to claim 1 wherein the somatostatin agonist is



wherein

A^1 is a D- or L- isomer of Ala, Leu, Ile, Val, Nle, Thr, Ser, β-Nal, β-Pal, Trp, Phe, 2,4-dichloro-Phe, pentafluoro-Phe, p-X-Phe, or o-X-Phe, wherein X is CH_3, Cl, Br, F, OH, OCH_3 or NO_2;

A^2 is Ala, Leu, Ile, Val, Nle, Phe, β-Nal, pyridyl-Ala, Trp, 2,4-dichloro-Phe, pentafluoro-Phe, o-X-Phe, or p-X-Phe, wherein X is CH_3, Cl, Br, F, OH, OCH_3 or NO_2;

A^3 is pyridyl-Ala, Trp, Phe, β-Nal, 2,4-dichloro-Phe, pentafluoro-Phe, o-X-Phe, or p-X-Phe, wherein X is CH_3, Cl, Br, F, OH, OCH_3 or NO_2;

A^6 is Val, Ala, Leu, Ile, Nle, Thr, Abu, or Ser;

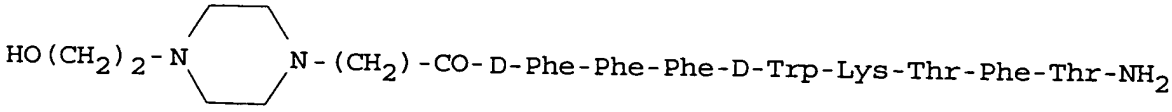
A^7 is Ala, Leu, Ile, Val, Nle, Phe, β-Nal, pyridyl-Ala, Trp, 2,4-dichloro-Phe, pentafluoro-Phe, o-X-Phe, or p-X-Phe, wherein X is CH_3, Cl, Br, F, OH, OCH_3 or NO_2;

A^8 is a D- or L-isomer of Ala, Leu, Ile, Val, Nle, Thr, Ser, Phe, β-Nal, pyridyl-Ala, Trp, 2,4-dichloro-Phe, pentafluoro-Phe, p-X-Phe, or o-X-Phe, wherein X is CH_3, Cl, Br, F, OH, OCH_3 or NO_2;

each R_1 and R_2, independently, is H, lower acyl or lower alkyl; and R_3 is OH or NH_2; provided that at least one of A^1 and A^8 and one of A^2 and A^7 must be an aromatic amino acid; and further provided that A^1, A^2, A^7 and A^8 cannot all be aromatic amino acids.

25. A method according to claim 24 wherein the linear somatostatin agonist is
H-D-Phe-p-chloro-Phe-Tyr-D-Trp-Lys-Thr-Phe-Thr-NH_2,
H-D-Phe-p-NO_2-Phe-Tyr-D-Trp-Lys-Val-Phe-Thr-NH_2,
H-D-Nal-p-chloro-Phe-Tyr-D-Trp-Lys-Val-Phe-Thr-NH_2,
H-D-Phe-Phe-Phe-D-Trp-Lys-Thr-Phe-Thr-NH_2 ,
H-D-Phe-Phe-Tyr-D-Trp-Lys-Val-Phe-Thr-NH_2,
H-D-Phe-p-chloro-Phe-Tyr-D-Trp-Lys-Val-Phe-Thr-NH_2 or
H-D-Phe-Ala-Tyr-D-Trp-Lys-Val-Ala-β-D-Nal-NH_2.

26. A method according to claim 1 wherein the somatostatin agonist is



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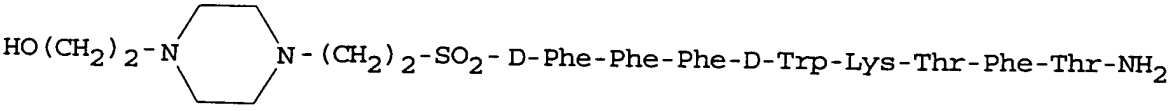

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PATENT COOPERATION TREA

09/423684

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

LUNT, Mark G.
DIBB LUPTON ALSOP
Fountain Precinct
Balm Green
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MGL

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT
(PCT Rule 71.1)

Date of mailing *(day/month/year)*	18. 08. 99

Applicant's or agent's file reference	IMPORTANT NOTIFICATION
P70920WO	

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP98/02999	13/05/1998	13/05/1997

Applicant
SOCIETE DE CONSEILS DE RECHERCHES ET ... et al

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/

European Patent Office
D-80298 Munich
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Authorized officer

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PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
P70920WO		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP98/02999	13/05/1998	13/05/1997
International Patent Classification (IPC) or national classification and IPC A61K38/31		
Applicant SOCIETE DE CONSEILS DE RECHERCHES ET ... et al		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 2 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☒ Certain documents cited
   - VII ☒ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
23/11/1998	18.08.99
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. (+49-89) 2399-0 Tx: 523656 epmu d Fax: (+49-89) 2399-4465	Authorized officer Pilling, S Telephone No. (+49-89) 2399 8461

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP98/02999

I. Basis of the report

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

Description, pages:

1-25	as originally filed				

Claims, No.:

1-25,26 (part)	as originally filed				
26 (part),27-37	as received on	26/07/1999	with letter of	20/07/1999	

2. The amendments have resulted in the cancellation of:

☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-32, 35, 36
	No:	Claims	33, 34, 37
Inventive step (IS)	Yes:	Claims	7, 9,
	No:	Claims	1 to 6, 8, 10-32, 35, 36
Industrial applicability (IA)	Yes:	Claims	33-37 (for Claims 1 to 32 see paragraph 2 of SECTION V on separate sheet)
	No:	Claims	

2. Citations and explanations

see separate sheet

VI. Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

SECTION V

1. The present application relates to methods of decreasing bodyweight using somatostatin or an agonist thereof (see Claims 1 to 32), compositions comprising somatostatin or an agonist thereof (see Claims 33, 34 and 37) and the use of somatostatin or an agonist thereof in the formulation of a composition for use in reducing excessive body weight (see Claims 35 and 36).

2. Claims 1 to 32 relate at least in part to methods of treatment of the human or animal body by therapy. In this regard, for the assessment of these claims with respect to industrial applicability, no unified criteria exist in the PCT. Furthermore, patentability can be dependent on the formulation of the claims. The EPO, for example does not recognize as industrially applicable, the subject matter of claims directed to a method of treatment of the human or animal body or to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment. Therefore, no statement as to the industrial applicability of Claims 1 to 32 is made herein.

3. The documents cited in the International Search Report (ISR) are consecutively numbered D1 to D6 in the order of their listing. If not indicated otherwise, reference is made to the passages cited in said ISR.

4. The following document is additionally cited herein;

   D7: H-J S Huang *et al*, Supplement to Hypertension, Vol. 19, No. 1, 01.01.1992, pp I-101 to I-109

   Claims 1 to 32, 35 and 36; somatostatin or an agonist thereof for decreasing body weight

5. None of the cited documents directly discloses that somatostatin or agonists thereof are useful in decreasing body weight.

6. Thus, the subject matter of Claims 1 to 32, 35 and 36 is new (Article 33(2) PCT).

7. With reference to lack of inventive step, however: Document D5 (WO-A-96/35950) discloses that "*ligands selective for somatostatin type-5 receptor ("SSTR-5") are effective in inhibiting release of amylin from pancreas cells*" (see page 2 lines 18 to 21 in D5) thus reducing hyperamylinemia. It is further indicated in document D5 (see page 1 lines 18 to 24) that *"The presence of an abnormally high concentration of amylin in the blood, i.e. hyperamylinemia, has been found in..//.. obese patients (see Huang et al., Hypertension 19 (Supp. I) :101 (1992)), ..Etc".* On turning to "*Huang et al*" (, *i.e.* document D7, see particularly page 107 therein) it is concluded therein that *"The present studies indicate that hyperamylinamia is not simply a passive partner to hyperinsulinemia. Rather, it could act as a causative mechanism of insulin resistance and associated metabolic derangements including obesity..Etc".* Hence, document D5 teaches that somatostatin type-5 receptor agonists reduce hyperamylinamia while document D7 teaches that hyperamylinamia plays a causative role in producing obesity. Thus, since the teachings of document D5 and D7 would clearly be considered together (since document D7 is cited in document D5), it is considered that the skilled man would be motivated to use somatostatin type-5 receptor agonists in the treatment of obesity in general. Hence, the subject matter of Claims 1 to 6, 8, 10 to 32, 35 and 36 lacks inventive step (Article 33(3) PCT).

8. With reference to the above points, it is acknowledged that the biochemical pathways responsible for obesity are complex and not fully elucidated. It is also noted however, that enough information concerning the functioning of these pathways was available before the priority date of the present application to enable the skilled man to predict with a reasonable degree of confidence that somatostatin-5 agonists would be useful in the treatment of obesity.

9. Furthermore, the present findings concerning lowering of plasma triglycerides in obese Zucker rats (see the present examples) appear to merely be a discovery relating to the mode of action of the obvious methods of present Claim 1.

10. None of the cited documents suggest or point towards the use of somatostatin type-2 selective receptor agonists for decreasing body weight in a patient. Hence, the subject matter of Claims 7 and 9 appears to be inventive (Article 33(3) PCT).

Claims 33, 34 and 37; compositions comprising somatostatin or an agonist thereof

11. Document D1 discloses pharmaceutical compositions (see page 6 line 34 to page 7 line 6 in D1) comprising somatostatin agonists such as *"H_2-c[-Cys-Phe-Phe-D-Trp-Lys Thr-Phe-Cys-NH_2"* (see page 6 lines 7 to 11 in D1 and compare with the compound of present Claim 33 and also the compound listed in present Claim 23 at page 32 line 5).

12. Similarly documents D5 and D6 (EP-A-0657174) disclose further pharmaceutical compositions comprising somatostatin or somatostatin agonists.

13. With reference to the comments set out in the preceding two paragraphs, it is noted that Claims 33, 34 and 37 are directed to pharmaceutical compositions *per SE* rather than methods of using said compositions.

14. Thus, the subject matter of Claims 33, 34 and 37 is not new in view of the disclosures of each of documents D1, D5 or D6 (Article 33(2) PCT).

SECTION VI

15. In view of the unavailability of the present priority documents it has not been possible for the IPEA to establish if the present claims are entitled to their earliest declared priority date. The present assessment of novelty and inventive step has been made on the assumption that the claims are entitled to their earliest declared priority date. The following documents (D3 and D4) may, however be considered to be relevant earlier applications in proceedings before certain authorities (see the states designated in respect of these earlier applications). Thus, it may be helpful to note that document D3 is potentially relevant to lack of novelty of Claims 1 to 10, 12 to 25, 27 to 37 while document D4 is potentially relevant to lack of novelty of Claims 1 to 10, 12 to 23, 27 to 37.

D3: WO-A-98/10786 published on 19.03.1998 filed on 10.09.1997 claiming priority from two previous applications filed on 12.09.96 and 10.10.96.

D4: WO-A-98/09991 published on 12.03.1998 filed on 04.09.1997 claiming priority

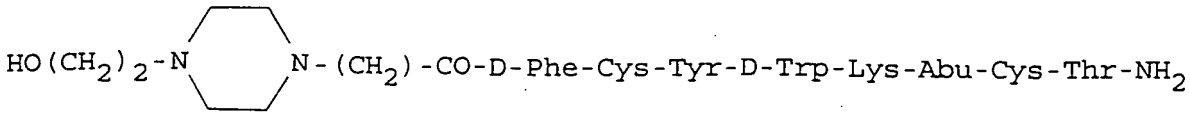
from a previous application filed on 05.09.1996.

SECTION VII

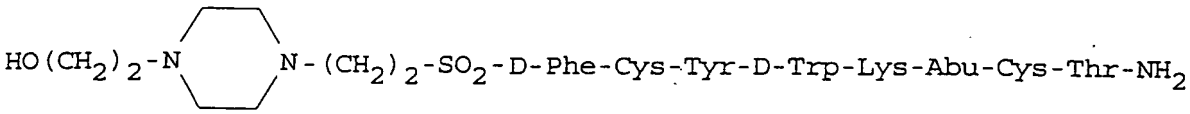
16. Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in documents D1 and D5 is not mentioned in the description, nor are these documents identified therein.

SECTION VIII

17. The further features of Claim 12 are repeatedly recited in Claims 13 to 22. Evidently, it would be possible to delete Claims 13 to 22 and make Claim 12 appendant to Claims 1 to 11. Thus, Claims 12 to 22 are considered to lack conciseness (Article 6 PCT). Similar considerations apply in respect of the further features of Claims 27 to 32



or



27. A method according to claim 1 wherein said patient is obese.

28. A method according to claim 3 wherein said patient is obese.

29. A method according to claim 4 wherein said patient is obese.

30. A method according to claim 7 wherein said patient is obese.

31. A method according to claim 8 wherein said patient is obese.

32. A method according to claim 11 wherein said patient is obese.

33. A pharmaceutical or cosmetic composition comprising a therapeutically or cosmetically effective amount of somatostatin; or a somatostatin agonist; or H-Cys-Phe-Phe-D-Trp-Lys-Thr-Phe-Cys-NH_2 wherein a disulfide bond exists between the free thiols of the two Cys residues.

34. A pharmaceutical composition as claimed in claim 33 having the features identified in any one of claims 3 to 10 and 23 to 26.

35. Use of a somatostatin, or a somatostatin agonist; or H-Cys-Phe-Phe-D-Trp-Lys-Thr-Phe-Cys-NH_2 wherein a disulfide bond exists between the free thiols of the two Cys residues, in the formulation of a pharmaceutical or cosmetic composition for use in reducing excessive body weight in a human or mammalian animal.

36. Use of a somatostatin, or a somatostatin agonist according to claim 35, wherein said somatostatin or somatostatin agonist has the relevant features identified in any one of claims 3 to 10 and 23 to 26.

37. A pharmaceutical composition substantially as hereinbefore described with reference to the Examples.

I[redacted]ENT COOPERATION TREATY

PCT

09/423684

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION**	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
P70920WO		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/EP 98/ 02999	13/05/1998	13/05/1997
Applicant		
SOCIETE DE CONSEILS DE RECHERCHES ET D'A..et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 4 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. [X] **Certain claims were found unsearchable** (see Box I).

2. [ ] **Unity of invention is lacking** (see Box II).

3. [ ] The international application contains disclosure of a **nucleotide and/or amino acid sequence listing** and the international search was carried out on the basis of the sequence listing
   - [ ] filed with the international application.
   - [ ] furnished by the applicant separately from the international application,
     - [ ] but not accompanied by a statement to the effect that it did not include matter going beyond the disclosure in the international application as filed.
   - [ ] Transcribed by this Authority

4. With regard to the **title,**
   - [ ] the text is approved as submitted by the applicant
   - [X] the text has been established by this Authority to read as follows:

   SOMATOSTATIN AND SOMATOSTATIN AGONISTS FOR DECREASING BODY WEIGHT

5. With regard to the **abstract,**
   - [X] the text is approved as submitted by the applicant
   - [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this International Search Report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is:

   Figure No. _____
   - [ ] as suggested by the applicant.
   - [ ] because the applicant failed to suggest a figure.
   - [ ] because this figure better characterizes the invention.
   - [X] None of the figures.

INTERNATIONAL SEARCH REPORT

[redacted]ational application No.
PCT/EP 98/02999

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Although claims 1 - 32
are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 98/02999

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K38/31 A61K7/48

According to International Patent Classification(IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 97 11962 A (BIOMEASURE INC ;UNIV TULANE (US); COY DAVID HOWARD (US); TAYLOR JO) 3 April 1997 see page 1, line 1 - line 29 see page 3 - page 4 see page 6, line 12 - line 23 see page 7, line 30 - line 34 ---	33-37
X	CARRETTA R ET AL: "REDUCTION OF BLOOD PRESSURE IN OBESE HYPERINSULINAEMIC HYPERTENSIVE PATIENTS DURING SOMATOSTATIN INFUSION" JOURNAL OF HYPERTENSION, vol. 7, no. SUPPL. 06, 18 June 1989, page S196/S197 XP002053034 see the whole document ---	33,34,37
	-/--	

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
21 September 1998	30/09/1998

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Fernandez y Branas,F

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	WO 98 10786 A (COHEN YAROM) 19 March 1998 see the whole document	1-37
X,P	WO 98 09991 A (UNIV WASHINGTON ;ZYMOGENETICS INC (US)) 12 March 1998 see page 8, line 33 - line 12 see page 30, line 19 - line 25	1,2,12, 13,27, 33,35,37
X	WO 96 35950 A (UNIV BUCKINGHAM) 14 November 1996 see the whole document	33,34,37
X	EP 0 657 174 A (MAYO FOUNDATION) 14 June 1995 see the whole document	33,34,37

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 98/02999

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9711962 A	03-04-1997	US 5708135 A	13-01-1998
		AU 6914596 A	17-04-1997
		EP 0859785 A	26-08-1998
		NO 981395 A	27-03-1998
WO 9810786 A	19-03-1998	AU 4133997 A	02-04-1998
WO 9809991 A	12-03-1998	AU 4250397 A	26-03-1998
WO 9635950 A	14-11-1996	US 5763200 A	09-06-1998
		AU 694360 B	16-07-1998
		AU 5764596 A	29-11-1996
		CA 2220106 A	14-11-1996
		EP 0829011 A	18-03-1998
EP 0657174 A	14-06-1995	US 5583104 A	10-12-1996